

# 5-Fluorouracil, A Tool in the Treatment of Skin Cancer and Keratoses\*

REUVEN K. SNYDERMAN

*Memorial Sloan-Kettering Cancer Center, New York, New York 10021*

Recently interest has arisen in the topical use of chemotherapeutic agents for the treatment of skin cancers and keratoses. Dr. Edmund Klein and his group at the Roswell Park Memorial Institute in Buffalo, New York, carried out extensive work in the study of the following drugs: Actinomycin D, Methotrexate, Spiramycin, Nitrogen Mustard, 5-Mercaptouracil, Dimethylurethimine and 5-Fluorouracil in an acid mantle cream. The results showed that many of these chemotherapeutic agents were able to attack the altered cell of keratosis and skin cancer and produce a destruction of the lesion.

The results showed that 20% 5-Fluorouracil in an acid mantle cream proved to be the most effective agent in the treatment of solar keratoses and skin cancer.

## Preparation of Ointment

The 20% 5-Fluorouracil ointment is prepared as follows: The 5-Fluorouracil crystalline powder is micronized in a high speed grinder and sieved through a #100 mesh screen so that the particles are less than  $150\mu$  in size. The powder is then intimately levigated with a small amount of base using a triple roller ointment mill.

This is then diluted to the desired concentration of 20% and is then mixed for at least one hour using a large Hobart mixer. The vehicle is Acid Mantle Creme of Dome Laboratories.

\*Presented at Tumor Grand Rounds, December 5, 1967, the Medical College of Virginia, Richmond.

## Protocol

Over two years ago a protocol was set up in Memorial Sloan-Kettering Cancer Center to study the effect of 20% 5-Fluorouracil in an acid mantle cream base in the treatment of patients with keratoses and skin cancers.

The patients who have been treated have had the disease for from 5 to 30 years, and all have had the usual modalities of treatment—surgery, x-ray, dessication and scraping. They frequently are able themselves to detect new lesions before their own physician finds them, and they are willing to try any form of treatment which can hold out some promise to them.

Each new patient had the nature of the disease and the form of treatment carefully discussed with him. As the drug is Federal Drug Administration controlled, he was asked to sign a release which stated that he realized this was an investigative project. If possible, a biopsy was obtained, or the biopsy report from his referring doctor was accepted. The area to be treated was photographed. The patient was instructed to apply the ointment twice a day and to wash it off gently before reapplying it. However, this was only possible during the early stages of the treatment.

## Treatment

When the patient presented himself with an entire face covered with keratoses and skin cancers, the usual anatomical sections of

the face, such as the forehead, half the face, the nose, etc., were treated separately.

The usual sequence of treatment is as follows: By the fourth to seventh day, an area of erythema appears. This occurs not only around those areas which were clinically suspicious, but also in other areas which the examiner may not have noted. It is thus believed that the drug has an affinity to find and attack the altered cell. From the seventh to 21st days the erythema increases. There will be some superficial ulceration, and crusting will start. Treatment is continued to 30 days. When areas of the face are being treated, they are left open to the air. In areas normally covered by clothes, a simple 4" × 4" dressing with paper tape is applied. When occlusive dressing is used, the reaction is much more marked. At the end of 30 days, treatment is discontinued. The crust is allowed to separate, and a pink surface remains which is quite similar to that produced by superficial abrasion.

There have been no systemic complications whatsoever. Blood counts which were studied in the early cases showed no alteration. The patients have complained of pain and a burning sensation. The simultaneous application of 20% Cortisone preparation has lessened this problem. Occasionally there will be marked edema around the eyes, which can be controlled by antihistamines. The most difficult problem is the appearance of the patient. Those who have a severe

facial reaction, especially men, whose beards tend to grow through the crust, will look frightful. However, the patient's weekly visit serves as a time to reassure him.

Upon completion of one area, a period of time is allowed for evaluation. Then, usually, with the patient freely giving his opinion, we are able to determine whether he chooses to go on and have another area treated. It is to be noted that the skin, after treatment, is softer, and many fine lines also disappear. This is rather encouraging to the women patients, but this is only temporary edema, and with time the fine lines again return. Most of the patients who need further treatment are anxious to go on, as they were pleased with the results.

When a second course of treatment is given, the response is quicker and more severe. The erythema will be produced by the second and third day, and ulceration and crusting will start by the seventh to tenth day. The patient has probably been made sensitive to the drug by the first treatment, and the second treatment elicits a much quicker response. In the future we will be able to take advantage of this reaction by reducing the length of time of the treatment or, possibly, by reducing the concentration of the ointment. In those cases which we have now given a third course of treatment, the reaction is even more accelerated. The ointment has an affinity for the altered cell and does not attack normal skin. When placed over an entire area, such as the forehead, the appearance is one of mottling with areas of erythema, and normal skin remains untouched in between.

We have advised the patients to keep the ointment away from the mucous membranes of the eyes, mouth, and nose. However, I know that on a number of occasions the patients have gotten the ointment on the various mucous membrane surfaces, and there has been no untoward reaction. We do not feel

that the ointment should be used over bare cartilage or bone.

In the beginning we were hesitant in using 5-FU in the treatment of radiation dermatitis and radiation-induced cancer. To date we have treated three patients with the disease and find a remarkably good response.

## Results

In over 100 cases now treated at Memorial Sloan-Kettering Cancer Center, the response has been excellent. However, these are patients who for many years have developed new lesions. The ointment is only able to remove keratoses and basal cell carcinomas which are present. It does not alter the fundamental makeup of the skin, and it must be expected that the patient will go on and develop new lesions. However, the patients who have undergone the treatment are extremely grateful for being freed of their problem for a period of time, whether this be a year, or two, or longer. The treatment can be repeated any time that new lesions appear.

The individual basal cell cancer can still best be treated by surgical excision. It is when one is presented with the multicentric basal cell problem and where surgery becomes an almost impossible task that 5-FU becomes a useful tool.

## Summary

1. 20% 5-Fluorouracil ointment in an acid mantle cream base is a useful tool for the treatment of multiple basal cell carcinomas and keratoses.
2. The method of treatment to date is application twice a day for a period of 30 days.
3. A second course of treatment can be applied to the same area or to other areas. A more severe reaction occurs with the second and third course of treatment.
4. The treatment removes the lesions which are present but in

no way alters the skin, and those disposed to develop new lesions will probably continue to do so in the future.